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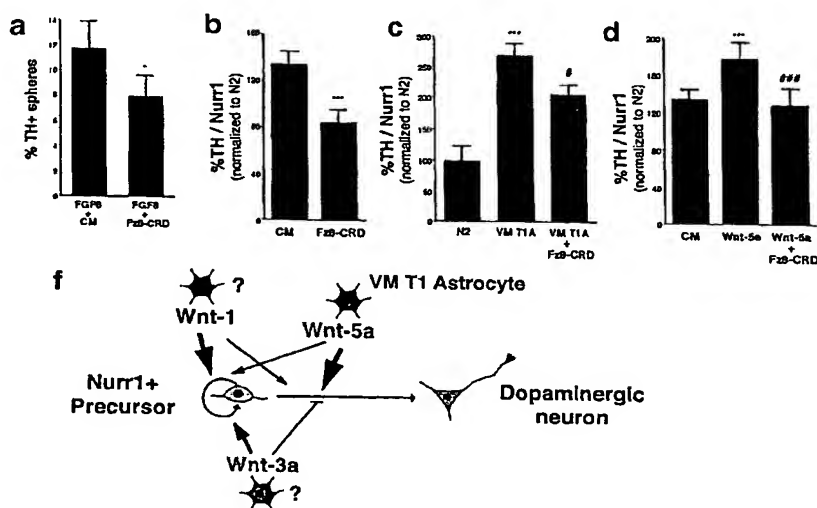
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[Continued on next page]

(54) Title: METHODS FOR PROMOTING DOPAMINERGIC NEURONAL DEVELOPMENT BY USING NG4A-SUBFAMILY AND WNT-LIGANDS



(57) Abstract: Methods for promoting dopaminergic neuronal development and producing neural cells having a dopaminergic phenotype. Dopaminergic neural cells may be used for treating individuals having a neurodegenerative disease such as Parkinson's disease. Dopaminergic cells may be implanted into the brain of the individual, and/or dopaminergic neural development may be induced or enhanced in the brain of the individual. Methods comprise expressing a nuclear receptor of the NG4A subfamily, e.g. Nurr1, above basal levels within the cell and treating the cell with a Wnt ligand, thereby producing or enhancing proliferation, self-renewal, survival and/or dopaminergic induction, differentiation, survival or acquisition of a neuronal dopaminergic phenotype. The cell may be co-cultured with astrocytes or glial cells and may be contacted with an FGF growth factor.



European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/04598

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/00 C12N15/06 C12N15/09 A61K35/30 G01N33/50  
C12Q1/68 A61P25/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, CHEM ABS Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TANG K ET AL: "Wnt-1 promotes neuronal differentiation and inhibits gliogenesis in P19 cells." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS. UNITED STATES 26 APR 2002, vol. 293, no. 1, 26 April 2002 (2002-04-26), pages 167-173, XP002272350 ISSN: 0006-291X figure 4	2-30, 40-43, 46-49, 52-64
Y	US 6 277 820 B1 (YE WEILAN ET AL) 21 August 2001 (2001-08-21)  column 1, line 60 -column 34, line 60 --- -/--	2-30, 40-43, 46-49, 52-64

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

4 March 2004

Date of mailing of the international search report

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Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/04598

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 58451 A (SALK INST FOR BIOLOGICAL STUDI) 5 October 2000 (2000-10-05)  claims 1-65  ---	2-30, 40-43, 46-49, 52-64
A	BHAT K M ET AL: "Sloppy paired acts as the downstream target of wingless in the Drosophila CNS and interaction between sloppy paired and gooseberry inhibits sloppy paired during neurogenesis." DEVELOPMENT (CAMBRIDGE, ENGLAND) ENGLAND FEB 2000, vol. 127, no. 3, February 2000 (2000-02), pages 655-665, XP002272351 ISSN: 0950-1991 page 659, column 2  ---	2-30, 40-43, 46-49, 52-64
A	WAGNER J ET AL: "Induction of a midbrain dopaminergic phenotype in Nurrl-overexpressing neural stem cells by type 1 astrocytes." NATURE BIOTECHNOLOGY. UNITED STATES JUL 1999, vol. 17, no. 7, July 1999 (1999-07), pages 653-659, XP002272352 ISSN: 1087-0156 figures 1-7  ---	2-30, 40-43, 46-49, 52-64
A	WO 00 66713 A (KAROLINSKA INNOVATIONS AB ;AAKERUD PETER (SE); ARENAS ERNEST (SE);) 9 November 2000 (2000-11-09)  claims 1-59  ---	2-30, 40-43, 46-49, 52-64
A	WO 00 29550 A (CESTE MARIE ;MCKAY RON (US); STUDER LORENZ (US); DOYLE JOHN (US);) 25 May 2000 (2000-05-25)  claims 1-62  ---	2-30, 40-43, 46-49, 52-64
E	US 2003/211605 A1 (LEE SANG-HUN ET AL) 13 November 2003 (2003-11-13)  claims 1-46  ---	2-30, 40-43, 46-49, 52-64
P,A	US 6 610 540 B1 (CSETE MARIE ET AL) 26 August 2003 (2003-08-26)  claims 1-11  ---  -/--	2-30, 40-43, 46-49, 52-64

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB 03/04598

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 01 88100 A (SASAI YOSHIKI ; KYOWA HAKKO KOGYO KK (JP)) 22 November 2001 (2001-11-22)</p> <p>abstract</p> <p>-----</p>	<p>2-30, 40-43, 46-49, 52-64</p>

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 03/04598

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 31-39, 50-51, 65-67  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☒ Claims Nos.: 44-45  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Claims Nos.: 31-39, 50-51, 65-67

Claims 31-39, 50-51 and 65-67 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

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## Continuation of Box I.2

Claims Nos.: 1

Present claims 1 relates to a method for inducing or promoting dopaminergic neuronal development by enhancing proliferation, self-renewal, induction, survival, differentiation and/or maturation in a neural cell.

Claim 1 covers a method for several cellular processes having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lacks clarity (Article 6 PCT). An attempt is made to define the methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the methods on page 71(description) and figures 1-10 relating to differentiation in a neuronal cell.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/04598

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 0058451	A	05-10-2000	US 6312949 B1 06-11-2001 AU 3767700 A 16-10-2000 WO 0058451 A1 05-10-2000
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